REMARKS

Specification

The specification at page 7, line 21 through page 8, line 2 has been amended so that the panels of Figure 4 are each separately designated. The specification at page 22 and 81 has been amended to correct informalities. No new matter has been added by these amendments.

Drawings

The drawings were objected to for the reasons set forth on the form PTO-948. One item indicated on this form concerns the petition to accept colored drawings. Applicant notes that a petition (and three copies of the colored drawings, Figures 4-11) were submitted on January 31, 2002, at the time the application was filed.

Substitute Formal Drawings are enclosed herewith. Applicant believes that these Drawings correct the objections raised by the Form PTO-948.

Status of Claims

Applicants have canceled claims 2-6, 8-14, 16-20, 22 and 26-58 without prejudice to continued prosecution. Claims 1 and 15 have been amended. Claim 59 is newly added. No new matter has been added to the claims. Applicants respectfully request reconsideration and allowance of claims 1, 7, 15, 21, 23-25 and 59 in view of the above amendments and following remarks.

Support for the amendments to the claims can be found throughout the specification. For example, support for the phrase "purified" protein can be found at page 11, lines 5-24 of the specification. Support for new claim 59, for example, can be found in original claim 1 and 7.

Rejection of Claim under 35 U.S.C. § 101

The examiner rejected claim 1 under 35 U.S.C. § 101 as being directed to non-statutory subject matter. Applicant has amended claim 1 as suggested by the examiner to clarify that the protein has been isolated from the remainder of the *N. gonorrhoeae* source material.

Rejection of Claims under 35 U.S.C. § 112, first paragraph

The examiner rejected claims 15, 19 and 21 (vaccine composition) under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Office Action at page 6 alleges that there is insufficient guidance to enable one skilled in the art to use the claimed compositions for the generation of a protective immune response against gonococcal disease caused by *Neisseria gonorrhoeae.*

The examiner has clearly identified the problem that the current invention addresses, which is an effective vaccine for *N. gonorrhoeae.* The human pathogen *N. gonorrhoeae* has a wide range of mechanisms that facilitate immune avoidance, including an antigenic shift in the expression of surface antigens. Because of this antigenic shift, the development of an effective vaccine has frustrated previous attempts (de la Paz, Microbiology 141:913-920 (1995)). Thus, the inventors developed a vaccine that would prevent the invasion and/or colonization by *N. gonorrhoeae.*

The inventors discovered that it is possible to prevent the infection of cervical cells (endocervical or ectocervical cells) by blocking the access of *N. gonorrhoeae* to the CR3 receptor on the surface of the cell (specification at page 48, lines 26 to page 49, line 2). They also found that *N. gonorrhoeae* invasion of endocervical and ectocervical cells is dependent on CR3 (specification at page 76, lines 15-29). Further, they isolated and purified the factors that were released by the gonococcus, including several proteins. One of these proteins, protein p55, which is the subject of the presently pending claims, was found to have enzymatic activity that involved modification of cellular phospholipid membranes (specification at page 79, lines 10-11). The inventors suggested that protein p55 was involved in the modification of the cell membrane to enhance entry of the gonococcus.

To confirm this assertion that p55 (which is also called "phospholipase D" or "PLD") was indeed involved in the modification of the cell membrane to enhance entry of the

gonococcus, the inventors present the results of their further experiments (*see* Declaration of Dr. Apicella under Rule 1.132). In these experiments, primary cervical cell monolayers were infected with gonococci. An anti-phospholipase D (PLD) antibody 1307 diluted 1:20 in RPMI1640 was added simultaneously with gonococci. After one hour of exposure to the primary human cervical epthelial cells, the ability of gonococci to adhere to and/or invade primary ecto- and endocervical cells was quantitatively determined using standard gentimicin-resistance assays. The total association (*i.e.*, adherence and invasion) of gonococci with primary ecto- and endocervical cells was quantitated by the omission of gentimicin from the above described invasion assay. Inhibition of gonococcal attachment and/or invasion was determined as a normalized function of the ability of gonococci to attach to and/or invade primary endo- and ectocervical cells in the absence of the inhibitors used (*i.e.*, antibody 1307).

The inventors found that treatment with the antiserum interferes with gonococcal association with the cervical epithelial cell with a reduction of approximately 70% (mean 28.13 to 7.92). There was no change in association of the PLD mutant in the presence or absence of antiserum (mean 14.84 to 14.37). Further, treatment with the antiserum interferes with gonococcal invasion of the cervical epithelial cell with a reduction of approximately 70% (mean 2.72 to 0.81). There was no change in association of the PLD mutant in the presence or absence of antiserum (mean 0.35 to 0.36).

Thus, the inventors have shown that protein p55 is involved in the modification of the cell membrane to enhance entry of the gonococcus. Further, they have shown that protein p55 can be used to generate antibodies that will interfere with gonococcal invasion, *i.e.*, provide protective immunity. Once the inventors taught that protein p55 would be effective in inducing a protective immune response, it would have been well within the skill of a person of ordinary skill in the art to produce a vaccine formulation, as taught by the specification at pages 43-48. The general principle of using proteins to induce immune responses effective (*e.g.*, antibodies) in protecting against colonization of bacterial pathogens was known by those of skill in the art at the time the application was filed. (*See, e.g.*, Thankavel *et al.*, J. Clin. Invest., 100:1123-1136 (1997)).

Thus, the examiner is requested to withdraw the rejection of claims 15, 19 and 21 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims under 35 U.S.C. § 112, second paragraph

The examiner rejected claims 1, 5 and 7 as being vague and indefinite under 35 U.S.C. § 112, second paragraph. Claim 5 has been canceled. Applicant has amended claim 1 to clarify that the claimed compound is an isolated 55 Kd protein (p55) from *N. gonorrhoeae.*

Thus, the examiner is requested to withdraw the rejection of claims 1 and 7 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims under 35 U.S.C. § 102(b)

The examiner rejected claims 1, 5, 7 and 15, 19, 21 and 23-25 as being anticipated under 35 U.S.C. § 102(b) by de la Paz *et al.*, Microbiology 141:913-920 (1995).

To constitute anticipation, the claimed subject matter must be identically disclosed in the prior art. *In re Arkley*, 172 U.S.P.Q. 524 at 526 (C.C.P.A. 1972). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. V. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 101 (Fed. Cir. 1991).

De la Paz *et al.* disclose outer-membrane proteins (OMP) from *N. gonorrhoeae* strain p9. The Examiner alleges at page 8, section 17 of the Office Action that "Outer membrane proteins (OMP) from *N. gonorrhoeae* would inherently contain the claimed protein and several other proteins that are linked together." Applicant respectfully disagrees with this allegation. The fraction OMP would not necessarily contain the claimed protein p55, if p55 were a secreted protein. Protein p55 is not an OMP. Protein p55 it is a secreted protein (*see*, Declaration of Dr. Apicella under Rule 1.132).

Further, de la Paz *et al.* do not teach or suggest a purified protein p55, nor SEQ ID NO:4, as recited by the pending claims. Therefore, de la Paz *et al.* do not teach or suggest the claimed invention.

Thus, the examiner is requested to withdraw the rejection of claims 1, 5, 7 and 15, 19, 21 and 23-25 as being anticipated under 35 U.S.C. § 102(b) by de la Paz *et al.*

Rejection of Claims under 35 U.S.C. § 102(b)

The examiner rejected claims 1, 5, 7, 15, 19, and 21 as being anticipated under 35 U.S.C. § 102(b) by Fraser *et al.*, Accession Number AAY 75751 (1999). The sequence Accession Number AAY 75751 was reported in PCT Publication WO 99/57280 as a deduced amino acid sequence ORF 987 (see page 1394-1395 of WO 99/57280, of record). Fraser *et al.* sequenced the *Neisseria meningitidis* and *N. gonorrhoeae* genomes, and then looked for open reading frames (ORFs). It is well known by those of skill in the art that ORFs may or may not actually code for functional proteins.

Fraser et al. do not teach or suggest all of the features of the pending claims. Fraser et al. do not teach purified proteins; they only teach putative ORFs, which might or might not encode a functional protein. It should be noted that this one ORF was just one of thousands of ORFs mentioned in this publication. It is clear that they did not know whether or not ORF 987 was expressed, and did not purify protein p55.

Thus, the examiner is requested to withdraw the rejection of claims 11, 5, 7, 15, 19, and 21 as being anticipated under 35 U.S.C. § 102(b) by Fraser *et al.*

Rejection of Claims under 35 U.S.C. § 102(a)

The examiner rejected claims 1, 5, 7, 15, 19, and 21 as being anticipated under 35 U.S.C. § 102(a) by Parkhill *et al.*, Accession Number B81859 (2000). The article associated with this nucleotide sequence is *Nature* 404:502-506 (2000).

Parkhill *et al.* disclosed the complete genomic sequence of a serogroup A strain of *Neisseria meningitidis* (NMA). The DNA was then compared with sequences in the EMBL database. From this BLAST search the found a region of the nucleic acid that had homology to a putative phospholipase D family protein (Accession Number B81859). They did not investigate whether B81859 was actually expressed in NMA. As discussed above, many ORFs and putative

genes are not actually expressed. Parkhill *et al.* did not investigate whether *N. gonorrhoeae* would have a region comparable to the putative gene in NMA. Nor did they investigate whether *N. gonorrhoeae* would have a similar nucleic acid sequence comparable to NMA, let alone a similar nucleic acid sequence that was actually expressed by *N. gonorrhoeae*. It is only with the hindsight of the present invention that one could know that such a nucleic acid sequence actually existed in *N. gonorrhoeae*, and that the nucleic acid was expressed by *N. gonorrhoeae*. Clearly, they did not purify the claimed protein p55.

Thus, the examiner is requested to withdraw the rejection of claims 11, 5, 7, 15, 19, and 21 as being anticipated under 35 U.S.C. § 102(b) by Parkhill *et al.*

Rejection of Claims under 35 U.S.C. § 102(b)

The examiner rejected claims 1, 5, 7,15, 19, 21 as being anticipated under 35 U.S.C. § 102(b) by Cann *et al.*, J. Med. Microbiology 30:23-30 (1989).

Cann *et al.* generally disclose antigens from *Neisseria*. Cann *et al.* did find that *N. meningitidis* had an antigen that was 55Kda in size. There is no further description of this antigen. It should be noted that in the Table on page 28 of the article that the authors did not see any 55Kda antigens from *N. gonorrhoeae*. Therefore, Cann *et al.* teach away from the claimed protein.

Thus, the examiner is requested to withdraw the rejection of claims 11, 5, 7, 15, 19, and 21 as being anticipated under 35 U.S.C. § 102(b) by Cann *et al.*

Enclosed is a check in the amount of $655 to cover the Petition for Extension of Time fee ($475) and the Information Disclosure Statement fee ($180). Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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